From: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
To: "Jinot, Jennifer"
Subject: RE: Ethylene Oxide Data
Date: Tuesday, December 9, 2014 10:38:09 AM
Attachments: DUA308d.docx

Jennifer,

I am not aware of any detailed report about the cohort study, but I can have a look. As for the data you are requesting, we can give you the analysis data files used for the papers with personal identifiers removed. According to the Privacy Act and the Freedom of Information Act (FOIA), I cannot release personally identifiable information on living individuals. Further, the death certificate data is exempted from release under FOIA also. NIOSH has received authorization under Section 308(d) of the Public Health Service Act, (42 U.S.C. 242 m (d)) to give assurance of confidentiality for death certificate data. This assurance applies to death certificates and the information thereon obtained from any entity for occupational health studies. Under the terms of the assurance of confidentiality, NIOSH would not be able to release from our studies any hardcopy or electronic copy of death certificates or death certificate information. However, we can provide a data file that has individual identifiers deleted, but that retains sufficient death certificate information to conduct statistical analyses, provided a data use agreement (DUA) is signed. Please keep in mind that some variables may be altered in the data files, in addition to removing direct identifiers, in order to protect privacy.

All people who would have access to the data and an official from their institution with authority for signing such agreements would need to sign the DUA. Therefore, in addition to any EPA employees who would have access, members of the SAB would also have to sign the DUA if they wish to see the data.

I have attached a blank DUA for you to complete if you wish to have the data. Please complete it at your earliest convenience. Once I receive a completed copy, we will begin to search our records for the requested data. This may take a little while. Also, please note the DUA will be in effect for three years from the date it was signed. After three years, the data must be destroyed, or a new DUA must be signed.

Please do not hesitate to contact me if you have any questions.

Brian

Brian Curwin, Ph.D.
Deputy Branch Chief
Industrywide Studies Branch
Division of Surveillance, Hazard Evaluations, and Field Studies
National Institue for Occupational Safety and Health
Centers for Disease Control and Prevention
1150 Tusculum Ave.

Mailstop R-13
Cincinnati, OH 45226
513-841-4432
bcurwin@cdc.gov

From: Jinot, Jennifer [mailto:Jinot.Jennifer@epa.gov]
Sent: Tuesday, December 02, 2014 12:06 PM
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Cc: Jinot, Jennifer
Subject: RE: Ethylene Oxide Data

hello, Brian. thanks for getting back to me. [redacted]

[redacted]

[redacted]

a final question that came up during our SAB review was whether or not there was a more-detailed report available from NIOSH about the cohort study. do you know if there is such a report?

please feel free to write or call me if you need any further details.

thanks!
jennifer jinot
U.S. EPA
703-347-8597

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS) [mailto:bic4@cdc.gov]
Sent: Monday, December 01, 2014 10:28 AM
To: Jinot, Jennifer

Subject: Ethylene Oxide Data

Hi,

I understand you are interested in Ethylene Oxide data. Could you please let me know what exactly you are interested in?

Thanks.

Brian

Brian Curwin, Ph.D.
Deputy Branch Chief
Industrywide Studies Branch
Division of Surveillance, Hazard Evaluations and Field Studies
National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention
4676 Columbia Parkway MS R-13
Cincinnati, Ohio 45226
Tel: 513-841-4432
Fax: 513-841-4486
email bcurwin@cdc.gov

From: Jinot, Jennifer
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Subject: RE: Ethylene Oxide Data
Date: Tuesday, December 9, 2014 10:57:29 AM

---

thanks, Brian. we will complete the form and get it back to you. we will also consult with our SAB officials to see what they want to do.
jennifer

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS) [mailto:bic4@cdc.gov]
Sent: Tuesday, December 09, 2014 10:38 AM
To: Jinot, Jennifer
Subject: RE: Ethylene Oxide Data

Jennifer,

I am not aware of any detailed report about the cohort study, but I can have a look. As for the data you are requesting, we can give you the analysis data files used for the papers with personal identifiers removed. According to the Privacy Act and the Freedom of Information Act (FOIA), I cannot release personally identifiable information on living individuals. Further, the death certificate data is exempted from release under FOIA also. NIOSH has received authorization under Section 308(d) of the Public Health Service Act, (42 U.S.C. 242 m (d)) to give assurance of confidentiality for death certificate data. This assurance applies to death certificates and the information thereon obtained from any entity for occupational health studies. Under the terms of the assurance of confidentiality, NIOSH would not be able to release from our studies any hardcopy or electronic copy of death certificates or death certificate information. However, we can provide a data file that has individual identifiers deleted, but that retains sufficient death certificate information to conduct statistical analyses, provided a data use agreement (DUA) is signed. Please keep in mind that some variables may be altered in the data files, in addition to removing direct identifiers, in order to protect privacy.

All people who would have access to the data and an official from their institution with authority for signing such agreements would need to sign the DUA. Therefore, in addition to any EPA employees who would have access, members of the SAB would also have to sign the DUA if they wish to see the data.

I have attached a blank DUA for you to complete if you wish to have the data. Please complete it at your earliest convenience. Once I receive a completed copy, we will begin to search our records for the requested data. This may take a little while. Also, please note the DUA will be in effect for three years from the date it was signed. After three years, the data must be destroyed, or a new DUA must be signed.

Please do not hesitate to contact me if you have any questions.

Brian

Brian Curwin, Ph.D.
Deputy Branch Chief
Industrywide Studies Branch
Division of Surveillance, Hazard Evaluations, and Field Studies
National Institue for Occupational Safety and Health
Centers for Disease Control and Prevention
1150 Tusculum Ave.
Mailstop R-13
Cincinnati, OH 45226
513-841-4432
bcurwin@cdc.gov

From: Jinot, Jennifer [mailto:Jinot.Jennifer@epa.gov]
Sent: Tuesday, December 02, 2014 12:06 PM
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Cc: Jinot, Jennifer
Subject: RE: Ethylene Oxide Data

hello, Brian. thanks for getting back to me. [redacted]

[redacted]

[redacted]

a final question that came up during our SAB review was whether or not there was a more-detailed report available from NIOSH about the cohort study. do you know if there is such a report?

please feel free to write or call me if you need any further details.

thanks!
jennifer jinot

U.S. EPA
703-347-8597

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS) [mailto:bic4@cdc.gov]
Sent: Monday, December 01, 2014 10:28 AM
To: Jinot, Jennifer
Subject: Ethylene Oxide Data

Hi,

I understand you are interested in Ethylene Oxide data. Could you please let me know what exactly you are interested in?

Thanks.

Brian

Brian Curwin, Ph.D.
Deputy Branch Chief
Industrywide Studies Branch
Division of Surveillance, Hazard Evaluations and Field Studies
National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention
4676 Columbia Parkway MS R-13
Cincinnati, Ohio 45226
Tel: 513-841-4432
Fax: 513-841-4486
email bcurwin@cdc.gov

From: Jinot, Jennifer
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Subject: RE: Ethylene Oxide Data
Date: Wednesday, December 17, 2014 3:00:38 PM

---

ok, thanks again for your reply. we will also request access to the JEM data when we submit our DUA form, and we will talk to Dr. Steenland.
jennifer

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS) [mailto:bic4@cdc.gov]
Sent: Wednesday, December 17, 2014 2:52 PM
To: Jinot, Jennifer
Subject: RE: Ethylene Oxide Data

Yes, you can have access to the JEM data, again only in a de-identified format. Please include that on your DUA form as well. Be as specific as possible about the data that you require. It will make it easier for us to find it.

Most of the people involved in the study no longer work for NIOSH, including the person who did the JEM. If you have questions, I would contact Kyle Steenland. He is now at Emory University. Unfortunately, we would be unable to provide any additional analysis.

Brian

From: Jinot, Jennifer [mailto:Jinot.Jennifer@epa.gov]
Sent: Wednesday, December 17, 2014 2:32 PM
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Cc: Jinot, Jennifer
Subject: RE: Ethylene Oxide Data

ok, great, thanks for your reply. we weren't sure whether it was needed for the mortality study or not, so it's good to know that it's not. i think that we have all the information we need now, so we will be providing the DUA form to our SAB and some panel members may be requesting access to the mortality study data. we intend to request access to the data for our own analyses as well. thanks for your help!

on another matter, an industry consultant, Robert Sielken, presented data regarding the ethylene oxide sterilizer worker job-exposure matrix at the SAB meeting that he had obtained from NIOSH under FOIA. would it be possible for us to receive the same information that he received? and we now have to address some concerns about the JEM that he raised at the meeting, so is it possible to get access to the JEM data? alternatively or additionally, might it be possible to contract with NIOSH so that someone there could do some analyses for us pertaining to the JEM? also, do you know if there is anyone still at NIOSH who worked on the exposure assessment for the sterilizer workers with whom we could speak? we are not certain yet how we are going to proceed to respond to some of the issues raised about the NIOSH study, but i am currently scoping out some possible options. thanks for your further assistance!

jennifer

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS) [mailto:bic4@cdc.gov]
Sent: Wednesday, December 17, 2014 2:18 PM
To: Jinot, Jennifer
Subject: RE: Ethylene Oxide Data

IRB stands for Institutional Review board and is used for Humans subject review. Typically we require an IRB approval for data involving living subjects such as a cancer incidence study. After looking more closely at your request, we can only provide the data for the mortality study, not the incidence study, and therefore an IRB approval is not necessary. Both studies have a 308(d) assurance of confidentiality. However, what we are allowed to do under the assurances of confidentiality are different. For the mortality data, we are allowed to release it in a de-identified format provided a DUA is signed. For the breast cancer incidence study, we cannot release any of the data unless consent is given by the subjects.

Brian

From: Jinot, Jennifer [mailto:Jinot.Jennifer@epa.gov]
Sent: Tuesday, December 16, 2014 4:53 PM
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Subject: FW: Ethylene Oxide Data

hi, Brian. i was wondering if you'd had a chance to consider our question about the IRB review. i go on jury duty on Thursday, and i'm not sure how long it's going to last, and i need to resolve this issue so that i can get back to our SAB with the DUA form. so if you could possibly let me know tomorrow morning, i'd really appreciate it. or if we need to talk about it, you can give me a call at 703-347-8597. thanks!
jennifer

From: Jinot, Jennifer
Sent: Thursday, December 11, 2014 11:48 AM
To: 'Curwin, Brian D. (CDC/NIOSH/DSHEFS)'
Subject: RE: Ethylene Oxide Data

hi, Brian. we do have a question about the data-use form. in the 4th paragraph, the form says "If the mortality data includes information on living subjects, appropriate IRB review of the proposed research and analysis is necessary." We were wondering what is meant by "IRB review" here and if it is applicable to the dataset used for the mortality study of the ethylene oxide cohort, as the cohort also includes living subjects. thanks!
jennifer

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS) [mailto:bic4@cdc.gov]
Sent: Tuesday, December 09, 2014 10:38 AM

To: Jinot, Jennifer
Subject: RE: Ethylene Oxide Data

Jennifer,

I am not aware of any detailed report about the cohort study, but I can have a look. As for the data you are requesting, we can give you the analysis data files used for the papers with personal identifiers removed. According to the Privacy Act and the Freedom of Information Act (FOIA), I cannot release personally identifiable information on living individuals. Further, the death certificate data is exempted from release under FOIA also. NIOSH has received authorization under Section 308(d) of the Public Health Service Act, (42 U.S.C. 242 m (d)) to give assurance of confidentiality for death certificate data. This assurance applies to death certificates and the information thereon obtained from any entity for occupational health studies. Under the terms of the assurance of confidentiality, NIOSH would not be able to release from our studies any hardcopy or electronic copy of death certificates or death certificate information. However, we can provide a data file that has individual identifiers deleted, but that retains sufficient death certificate information to conduct statistical analyses, provided a data use agreement (DUA) is signed. Please keep in mind that some variables may be altered in the data files, in addition to removing direct identifiers, in order to protect privacy.

All people who would have access to the data and an official from their institution with authority for signing such agreements would need to sign the DUA. Therefore, in addition to any EPA employees who would have access, members of the SAB would also have to sign the DUA if they wish to see the data.

I have attached a blank DUA for you to complete if you wish to have the data. Please complete it at your earliest convenience. Once I receive a completed copy, we will begin to search our records for the requested data. This may take a little while. Also, please note the DUA will be in effect for three years from the date it was signed. After three years, the data must be destroyed, or a new DUA must be signed.

Please do not hesitate to contact me if you have any questions.

Brian

Brian Curwin, Ph.D.
Deputy Branch Chief
Industrywide Studies Branch
Division of Surveillance, Hazard Evaluations, and Field Studies
National Institue for Occupational Safety and Health
Centers for Disease Control and Prevention
1150 Tusculum Ave.
Mailstop R-13
Cincinnati, OH 45226

513-841-4432
bcurwin@cdc.gov

From: Jinot, Jennifer [mailto:Jinot.Jennifer@epa.gov]
Sent: Tuesday, December 02, 2014 12:06 PM
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Cc: Jinot, Jennifer
Subject: RE: Ethylene Oxide Data

hello, Brian. thanks for getting back to me. [redacted]

[redacted]

[redacted]

a final question that came up during our SAB review was whether or not there was a more-detailed report available from NIOSH about the cohort study. do you know if there is such a report?

please feel free to write or call me if you need any further details.

thanks!
jennifer jinot
U.S. EPA
703-347-8597

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS) [mailto:bic4@cdc.gov]
Sent: Monday, December 01, 2014 10:28 AM
To: Jinot, Jennifer
Subject: Ethylene Oxide Data

Hi,

I understand you are interested in Ethylene Oxide data. Could you please let me know what exactly you are interested in?

Thanks.

Brian

Brian Curwin, Ph.D.
Deputy Branch Chief
Industrywide Studies Branch
Division of Surveillance, Hazard Evaluations and Field Studies
National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention
4676 Columbia Parkway MS R-13
Cincinnati, Ohio 45226
Tel: 513-841-4432
Fax: 513-841-4486
email bcurwin@cdc.gov

From: Jinot, Jennifer
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Subject: our DUA form
Date: Wednesday, December 24, 2014 11:26:47 AM
Attachments: NIOSH DUA for EtO - 24dec2014.pdf

---

hi, Brian. a hardcopy of our signed DUA form is in the mail, and we have sent the form to our SAB, so you may also be hearing from some of the panel members. thank you for all your help! i've attached a PDF of our signed form in case it is of any use to you. please let me know if you need any additional information. thanks!

jennifer
703-347-8597

SIGNATURES ***(add additional signature pages if needed)***

Principal requestor: (*same as specified in section "Supporting Information"*)
By signing this agreement, I attest to the accuracy of the information provided in this application and agree to abide by all of the terms and conditions of this agreement. My signature indicates my agreement to comply with the above-stated requirements with the knowledge of the potential penalties for violations noted above.

Printed Name: Jennifer Tinot

Signature: (b) (6) Date: 24 Dec 2014

Official of principal requestor's organization authorized to make agreements: (*same as specified in section "Supporting Information"*)
By signing this agreement on behalf of an institution, university, company or other organization, I am declaring that I am the individual who has the authority to make these assurances on behalf of and to bind this institution, university, company or other organization to the terms and conditions of this agreement. My signature indicates my agreement and my organization's agreement to comply with the above-stated requirements with the knowledge of the potential penalties for violations noted above.

Printed Name: Gina Perovich for Ken Olden

Signature: (b) (6) Date: 12/24/14

All other persons from this organization who will have access to all or part of the data: (*same as specified in list requested in section "Supporting Information"; add additional pages if needed*)
My signature indicates my agreement to comply with the above-stated requirements with the knowledge of the potential penalties for violations noted above.

(b) (6)

(Signature) 12/24/14 (Date)

(Signature) 12/24/14 (Date)

(Signature) (Date)

(Signature) (Date)

From: Corcoran, Melissa (CDC/NIOSH/DSHEFS)
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Subject: Ethylene Oxide Study
Date: Tuesday, November 25, 2014 10:38:22 AM

Brian,

I received a call from Jennifer Jinot from EPA requesting access to raw data for the Ethylene Oxide Study. Are you able to help her? She can be reached at 703.347.8597 or jinot.jennifer@epa.gov.

Thanks,

Melissa Corcoran
Branch Secretary
Industrywide Studies Branch
CDC/NIOSH/DSHEFS
Cincinnati, Ohio 45226
513-841-4436

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
To: Jinot, Jennifer
Subject: RE: our DUA form
Date: Wednesday, December 31, 2014 10:57:00 AM
Attachments: SKMBT_C55014122911530.pdf

Hi Jennifer, I have received your signed hard copy. We will begin locating and preparing the files. This may take a few weeks to complete Also, please find attached a copy of the industrial hygiene report on ethylene oxide exposure.

Brian

From: Jinot, Jennifer [mailto:Jinot.Jennifer@epa.gov]
Sent: Wednesday, December 24, 2014 11:27 AM
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Subject: our DUA form

hi, Brian. a hardcopy of our signed DUA form is in the mail, and we have sent the form to our SAB, so you may also be hearing from some of the panel members. thank you for all your help! i've attached a PDF of our signed form in case it is of any use to you. please let me know if you need any additional information. thanks!
jennifer
703-347-8597

INDUSTRIAL HYGIENE CHARACTERIZATION OF ETHYLENE OXIDE EXPOSURES OF HOSPITAL AND NURSING HOME WORKERS

Virginia L. Ringenburg
Larry J. Elliott
Paula Morelli-Schroth
Daniel Molina

U.S. Department of Health and Human Services
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health
Division of Surveillance, Hazard Evaluations, and Field Studies
Cincinnati, Ohio 45226

December, 1986

DISCLAIMER

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH).

Authors:

Virginia L. Ringenburg[1]
Larry J. Elliott[1]
Paula Morelli-Schroth[2]
Daniel Molina[1]

Affiliation:

1 Industrywide Studies Branch, Division of Surveillance, Hazard Evaluations and Field Studies (DSHEFS), the National Institute for Occupational Safety and Health (NIOSH), Cincinnati, Ohio

2 Occupational Safety and Health Administration (OSHA), Formally with Division of Surveillance, Hazard Evaluations and Field Studies (DSHEFS), the National Institute for Occupational Safety and Health (NIOSH), Cincinnati, Ohio.

ACKNOWLEDGEMENT

The authors thank all the participating facilities for their cooperation and for providing us with technical information and access to their facilities.

Sincere appreciation is extended to Mrs. Marianne Fleckinger and Ms. Nancy Rosenberger for their assistance in preparing this manuscript.

TABLE OF CONTENTS

	Page
Abstract	v
Introduction	1
Description of Facility, Workforce and Process	2
Table I - Hospital Summary Information	3
Figure 1 - Type 1 and Type 2 EtO Sterilizers	4
Figure 2 - Type 3 and Type 4 EtO Sterilizers	5
Applicable Standards and Recommended Levels	6
Description of Sampling and Analytical Methods	6
Results and Discussion	8
Exposures Below NIOSH/OSHA Criteria	8
Figure 3 - Personal 8-Hour TWA EtO Sampling Results (Range/Mean)	9
Figure 4 - Arithmetic Mean, Personal, Short-Term EtO Sampling Results	10
Table II - EtO Exposure Levels Relative to Engineering Controls and Work Practices	11
Area Concentrations Above/Exposures Below NIOSH/OSHA Criteria	12
Exposures Above NIOSH/OSHA Criteria	13
Conclusions	18
Recommendations	19
Engineering Controls	19
Work Practices	20
References	22
Appendix A - Toxicity of EtO	25
Appendix B - Personal Long-Term and Short-Term EtO Exposure Levels	29
Appendix C - Area Long-Term and Short-Term EtO Concentrations	46
Appendix D - Area Peak EtO Concentrations	71

From: Jinot, Jennifer
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Subject: data disc received
Date: Wednesday, February 11, 2015 11:34:04 AM

---

hi, Brian. so sorry. i thought i'd already written to let you know that we received the data, but when i went back to this old email i'd sent to you so that i could copy the address info for another purpose, i saw that i had apparently neglected to send you a follow-up email. so, anyway, we did receive it, and thanks!!! i haven't had a chance to look at it yet, as i've been busy on other things, including the memo to NIOSH requesting analyses of the breast cancer incidence data. we hope to have the memo to you soon. again, thanks!
jennifer

From: Jinot, Jennifer
Sent: Wednesday, January 28, 2015 1:00 PM
To: 'Curwin, Brian D. (CDC/NIOSH/DSHEFS)'
Subject: RE: our DUA form

hi, Brian. i hadn't received the data as of today, so i was going to try to track down the package when i realized that you only had the 1200 Pennsylvania Ave address, which is EPA's main headquarters address and the address of the mail room for USPS mail, but it is not a delivery address for FedEx. the package might still get to me by a circuitous route, but, most likely, it will get returned to you. i am providing a delivery address to you in case it does get returned so that you can please resend it to me.

Jennifer Jinot
U.S. EPA (7th floor, N-7337)
Two Potomac Yard
2733 South Crystal Drive
Arlington, VA 22202

and please make sure that they have my phone number (703-347-8597) in case there's any issue at the security desk.
thanks! and sorry for the mix-up!
jennifer

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS) [mailto:bic4@cdc.gov]
Sent: Monday, January 26, 2015 8:57 AM
To: Jinot, Jennifer
Subject: RE: our DUA form

Jennifer,

A CD with the data files is being sent to you via fed-ex today. It should arrive tomorrow. The CD is encrypted. The password is: (b)(6)

Let me know if you have any questions.

Brian

From: Jinot, Jennifer [mailto:Jinot.Jennifer@epa.gov]
Sent: Wednesday, December 24, 2014 11:27 AM
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Subject: our DUA form

hi, Brian. a hardcopy of our signed DUA form is in the mail, and we have sent the form to our SAB, so you may also be hearing from some of the panel members. thank you for all your help! i've attached a PDF of our signed form in case it is of any use to you. please let me know if you need any additional information. thanks!
jennifer
703-347-8597

From:	Jinot, Jennifer
To:	Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Cc:	Bussard, David
Subject:	EPA request for analyses of NIOSH ethylene oxide breast cancer incidence data
Date:	Tuesday, February 24, 2015 2:45:10 PM
Attachments:	memo to NIOSH_24feb2015.docx Libby Schoenfeld residuals example.docx SAB_CAAC_EtO_Report_010715 (1).pdf Carcinogenicity of EtO Appendices for SAB CAAC review_8-15-14_HERO.docx Carcinogenicity of EtO Main Report for SAB CAAC review_8-15-14_HERO.docx Steenland2003-epi-breastCA.pdf steenland2004.pdf

---

Hi, Brian. As we discussed on the phone, I have prepared a written request to NIOSH for the analyses we are hoping that NIOSH will perform. Please find attached this request as well as some supplemental reference materials pertaining to the request. If you have any questions or are in need of any further information, please do not hesitate to contact me (jinot.jennifer@epa.gov; 703-347-8597). Thank you! jennifer

MEMORANDUM

TO: Brian Curwin, Deputy Branch Chief, Industrywide Studies Branch, NIOSH

FROM: Jennifer Jinot, Assessment Manager for EPA's Ethylene Oxide Carcinogenicity Assessment, National Center for Environmental Assessment, U.S. EPA

RE: Request for analyses of the NIOSH ethylene oxide breast cancer incidence cohort dataset

DATE: 24 February 2015

Following our telephone conversation of 28 January 2015, this memo provides a written request to NIOSH for analyses of the NIOSH ethylene oxide breast cancer incidence cohort dataset (described in Steenland et al., 2003), as EPA is unable to obtain access to these incidence data to perform the analyses itself. This memo will provide some background context, a brief summary of the reasons for EPA's request, and a discussion of the analyses being requested.

In 2007, an external review draft of EPA's assessment of the carcinogenicity of ethylene oxide was reviewed by EPA's Science Advisory Board (SAB). The draft relied on published results from the exposure-response modeling analyses of the NIOSH ethylene oxide (sterilizer worker) cohort conducted and published by NIOSH (Steenland et al. [2003] for breast cancer incidence and Steenland et al. [2004] for cancer mortality) for the derivation of quantitative estimates of the cancer risk resulting from both environmental and occupational exposures to ethylene oxide. The SAB supported EPA's use of the NIOSH data but strongly recommended that additional analyses be done. In response to the SAB recommendations, EPA contracted with Kyle Steenland to conduct additional analyses of the mortality and the breast cancer incidence datasets for EPA.

In August 2014, EPA released a revised external review draft for review by the SAB. This revised draft relied on the additional analyses conducted by Dr. Steenland for the derivation of the cancer risk estimates. The SAB reviewed the revised draft in a public meeting in November 2014 and issued a draft report in January 2015. The SAB again supported EPA's use of the NIOSH data but strongly recommended that further details be provided about the exposure levels and other characteristics of the cohort and that sensitivity analyses be conducted related to some of the exposure-response analyses presented in the draft assessment. To this end, EPA has requested access to the mortality dataset and data related to the exposure assessment from NIOSH. However, because of restrictions on the breast cancer incidence data, EPA is unable to obtain access to the breast cancer incidence dataset.

Without the sensitivity analyses of the breast cancer incidence data, it would be difficult for EPA to be responsive to the SAB recommendations, and this could undermine the utility of EPA's assessment of the carcinogenicity of ethylene oxide. This assessment is needed to support EPA's regulatory efforts to protect the environment and public health. In addition to EPA's interest in risks resulting from environmental exposures to ethylene oxide, EPA also has a regulatory interest in the risks from occupational exposures arising from the sterilizer uses of

ethylene oxide, under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Therefore, EPA's assessment includes cancer risk estimates resulting from occupational exposure scenarios, as well as from environmental exposures to ethylene oxide. The NIOSH cohort data, including the breast cancer incidence data, are especially well-suited to inform EPA's assessment of the risks to sterilizer workers, as that is the population comprising NIOSH's ethylene oxide cohort.

As discussed in our telephone conversation, to help EPA complete its ethylene oxide carcinogenicity assessment and support its regulatory obligations, NIOSH has offered to consider conducting additional analyses of the breast cancer incidence dataset for EPA. EPA greatly appreciates this offer, and this memo provides a prioritized list of the analyses that EPA feels would be most responsive to the SAB recommendations. The requested analyses reflect a somewhat iterative process, in which the results of some analyses inform whether or not other analyses are warranted. Hopefully, the prioritized list is clear in this regard, but if any clarifications are needed, please let me know.

EPA has been in contact with Dr. Steenland regarding the feasibility of the analyses recommended by the SAB, and he has expressed a willingness to assist NIOSH in conducting any analyses of the breast cancer incidence data for EPA. This assistance might facilitate the analyses for NIOSH, as Dr. Steenland conducted the original analyses that would be the basis for the sensitivity analyses and he could provide SAS code and other insights pertaining to the sensitivity analyses.

In our telephone conversation, you suggested that Jim Deddens might be available to conduct these analyses for NIOSH. That sounds ideal, as he has already worked on this cohort with Dr. Steenland. I understand that Dr. Deddens might not be available for the next month or two, but that should not be a problem for EPA, as our timeframe is somewhat longer-term. If possible, we would appreciate having the results of any analyses that NIOSH would conduct for us by the end of August 2015.

Attached below is a list of the specific analyses being requested. Attached to the email conveying this memo, please find copies of EPA's draft ethylene oxide carcinogenicity assessment, the draft SAB report, and the Steenland et al. (2003, 2004) papers, for your reference. If you have any questions or are in need of any further information, please do not hesitate to contact me (jinot.jennifer@epa.gov; 703-347-8597). Thank you.

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

(b) (5)

Cancer Causes and Control **14**: 531–539, 2003.

Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States)

Kyle Steenland*, Elizabeth Whelan, James Deddens, Leslie Stayner & Elizabeth Ward
National Institute for Occupational Safety and Health (NIOSH), Cincinnati, Ohio

Received 9 October 2002; accepted in revised form 10 March 2003

Key words: breast cancer, ethylene oxide.

Abstract

Background: Ethylene oxide (ETO) is a sterilant gas considered to be a human carcinogen, due primarily to excess hematopoietic cancer in exposed cohorts. ETO causes mammary tumors in mice, and has been associated with breast cancer incidence in one small epidemiologic study.
Methods: We have studied breast cancer incidence in a cohort of 7576 women employed for at least one year and exposed for an average 10.7 years while working in commercial sterilization facilities. Breast cancer incidence (n = 319) was ascertained *via* interview, death certificates, cancer registries, and medical records. Interviews were obtained for 68% of the cohort.
Results: The standardized incidence ratio (SIR) for incident breast cancer in the whole cohort using external referent rates (SEER) was 0.87 (0.77–0.97). The SIR for those in the top quintile of cumulative exposure, with a 15 year lag, was 1.27 (0.94–1.69), with a positive trend of increasing SIR with increasing exposure ($p = 0.002$). SIRs are underestimated because breast cancer incidence in the whole cohort was under-ascertained, due to incomplete response and lack of complete coverage by state cancer registries. In internal nested case–control analyses of those with interviews (complete cancer ascertainment), controlling for reproductive risk factors, a positive exposure–response was found with the log of cumulative exposure with a 15-year lag ($p = 0.0005$). The odds ratio by quintile of cumulative exposure were 1.00 (0 exposure due to 15 year lag), 1.06, 0.99, 1.24, 1.42, and 1.87.
Conclusions: Our data suggest that ETO is associated with breast cancer, but a causal interpretation is weakened due to some inconsistencies in exposure–response trends and possible biases due to non-response and incomplete cancer ascertainment.

Introduction

Ethylene oxide (ETO) is widely used as a sterilant gas and an industrial chemical. NIOSH has estimated that approximately 270,000 people were exposed in the US in the 1980s, principally in hospitals (96,000) and commercial sterilization (21,000) [1]. Exposure levels to ETO in the US have decreased greatly since the early 1980s when a one ppm standard was instituted, based on early findings of leukemia in animals and humans.

ETO is a direct-alkylating agent which causes increased chromosomal aberrations and sister-chromatid exchange [2]. Inhaled ETO is quickly absorbed in the lungs and distributed rapidly throughout all tissues; it forms dose-related hemoglobin adducts in people and rodents, and dose-related DNA adducts in rodents [2]. The International Agency for Research on Cancer (IARC) has determined that ETO is a definite (Group 1) human carcinogen, based on limited evidence from epidemiologic studies showing increased hematopoietic cancer, supported by positive human cytogenetic evidence, and on sufficient evidence from animal studies for hematopoietic and other cancers [2].

Besides hematopoetic cancer, more recently there has been concern that ETO might also be linked to breast cancer, based on limited evidence. Norman *et al.* [3] found a statistically significant twofold increase in breast cancer incidence based on 12 observed cases among

* Address correspondence to: School of Public Health, NIOSH R13, Emory University, 1518 Clifton Road, NE, GA 30322 Atlanta, USA. Fax: +1-404-747-8744; E-mail: nsteenl@sph.emory.edu

women exposed at a commercial sterilization plant. A cluster of breast cancers was observed among Hungarian hospital workers exposed to ETO [4]. Furthermore, animal data indicated that ETO caused mammary tumors in mice [2], although not in rats. However, two other small incidence studies (together based on fewer than 10 cases) did not show an excess of breast cancer [5, 6]. Two mortality studies, one small [7] (four breast cancer deaths) and one large [8] (a NIOSH study of 10,000 women, 42 breast cancer deaths) also failed to show an excess. To study this issue further we have conducted a breast cancer incidence study of 7576 women from the NIOSH cohort employed for at least one year.

Methods

Cohort definition

This study of breast cancer incidence was based on the women in a US cohort of 18,000 men and women exposed for at least three months to ETO, from the 1940s to the 1980s. The original cohort was assembled by NIOSH in the mid-1980s, and has been previously studied for mortality [8]. Cohort members worked at 14 plants in 11 states.

Interviews

We sought cancer incidence information for 7576 women (76% of women in the original cohort) who had worked for at least one year. The restriction to those with at least one year employment was motivated by cost considerations and the greater difficulty of locating women with short term employment. Follow-up for breast cancer in the present study began no earlier than one year after the beginning of employment, or after three months of exposure, whichever date was later.

We sent a written questionnaire to all women, or their next-of-kin (18% of the cohort had died), for whom we could find valid addresses. After two mailings and a reminder postcard, we called non-respondents, at varying times of day and days of the week. When possible, the interview was then conducted by phone. Addresses and telephone numbers were identified using a variety of strategies including the Internal Revenue Service, the US Postal Service, motor vehicle registration, credit bureaus, and telephone number look-up services. The interview asked about ethnicity, education, height, weight, longest job, menstrual and reproductive history (including number and dates of pregnancies, and pregnancy outcomes), use of hormones, smoking history, alcohol history, diet, and cancer history (with extra detail on breast cancer).

Breast cancer ascertainment

Breast cancer cases were identified by the interview. In addition, ascertainment was also conducted *via* death certificates and cancer registries. Cancer registries were available in nine of the 11 states in which plants were located, but often for limited periods of time (Texas 1992, 1995–1997, Georgia 1975–1998 for Atlanta area, 1995–1998 for entire state, Kentucky 1991–1998, Maryland 1992–1998, Florida 1981–1998, New Jersey 1979–1998, Connecticut 1935–1998, South Carolina 1996–1998, New York 1976–1998). We matched women who had worked in a given state or contiguous state against cancer registries for that state; for Florida we matched the entire cohort under the assumption that women from any state may have retired there.

Medical record confirmation was sought for all cancers reported on interview. We also sought medical records for all decedents who died of cancer. However, cases identified by self-report or death certificates, for whom no medical record was obtained, were included in the analysis.

Follow-up methods and definition of end of follow-up

Mortality follow-up was extended beyond the previous 12/31/1987 until 12/31/1998, *via* Social Security, the Internal Revenue Service, and the National Death Index (NDI). Causes of death were obtained from NDI. Vital status for deaths prior to the existence of NDI (prior to 1979) were identified by Social Security and Internal Revenue Service records, and causes of death were obtained *via* death certificates obtained from states.

Follow-up for breast cancer incidence was likewise terminated as of 12/31/1998. Dates of diagnosis were obtained from self-report, medical record, cancer registry, or next-of-kin. In case of multiple dates the earliest and/or the date considered most valid was used. For breast cancer decedents for whom no other source was available, date of death was used as date of diagnosis. If a women or her next-of-kin reported breast cancer, but this report was specifically contradicted by medical record or cancer registry data, this woman was not included in the analysis as a case ($n = 6$). If a women or their next-of-kin did not report breast cancer on interview but breast cancer was found in the medical record or cancer registry record, then these women were included as a case ($n = 25$).

Exposure estimates

Estimated exposures over time for this cohort had been developed previously, based on a large number of

measurements coupled with data on historical process changes [9]. Exposure estimates covered all years during which employees were exposed, and were derived from a model which explained 85% of the variance of the observed sampling data. One small plant in the original cohort (19 women with more than one year employment) lacked exposure estimates, and was excluded from the present study.

Work history data had been gathered originally in the mid-1980s. Some plants in the study continued using ETO after this point, and for them we gathered additional information on the date-last-employed for those who had been employed at the time work history was collected (25% of the cohort). Work history for these women was extended until the date-last-employed at the plant in question; it was assumed that they did not change jobs and that the level of ETO exposure remained the same as in their last job in the mid-1980s. Cumulative exposure calculated with and without the extended work histories differed little because exposures were very low by the mid-1980s.

Analyses using the full cohort and an external comparison

Breast cancer incidence was analyzed in the entire cohort (n = 7576) *versus* an external non-exposed population (the SEER population). Ascertainment of breast cancer in the entire cohort was known to be incomplete, because some women did not have interviews and did not live in states with cancer registries. It was not possible to estimate the degree of under-ascertainment.

Life-table analyses of the entire cohort were done using the NIOSH Life-Table Analysis system [10] (www.cdc.gov/niosh/ltdoc.html), using referent rates developed from SEER (Surveillance, Epidemiology, and End Results) data for the period 1970–1999, for invasive female breast cancer (ICD 9th revision code 174) and *in situ* breast cancer (ICD 9th revision code 233.0). The SEER data represent approximately 10% of the US population.

Analyses using SEER referent rates produced standardized incidence ratios (SIRs) by categories of the cumulative exposure (ETO ppm-days), stratified by age (five year categories), calendar time (five year categories), and race/ethnicity (white and non-white). Follow-up time began in 1970 when the SEER rates begin, or one year after first employment, or at the date of first exposure plus 90 days (a requirement for cohort entry in the original study), whichever was later. The restriction of follow-up to the period post-1970 was presumed to have little effect on results because it eliminated only three percent of the breast cancer cases and seven percent of the person-time which would have been available without this restriction. Follow-up continued until date of death (or date of diagnosis, for breast cancer cases), end-of-study (12/31/1998), or date-last-observed for those lost-to-followup, whichever was earliest.

Categorical analyses by cumulative exposure (ETO ppm-days) using data from the life-table analyses were done by quintiles, based on the cases = cumulative exposure. Analyses with a 15 year lag were also conducted; a 15 year lag was chosen based on having the best fit to the data in internal regression analyses (see below). A 15 year lag discounts all exposure occurring with the last 15 years, and in some instances results in a case having no exposure ("lagged out"). Quintiles in lagged analyses were formed based on the cumulative exposure of all cases not "lagged out".

Trend tests for trends in SIRs with cumulative exposure (in which the lowest exposed group was the referent) were done *via* Poisson regression (SAS GENMOD [11]). For analyses using the log of cumulative exposure with a lag, a cumulative exposure of one ppm-day was added to everyone's cumulative exposure to avoid taking the logarithm of 0.

Breast cancer-*in situ* was reported for six percent of the cases (20/319). *In situ* and invasive cancer cases were analyzed separately when using external referent rates (SEER rates), and results then combined. *In situ* cases were likewise included in internal Cox regression analysis. Results did not differ greatly with the inclusion or exclusion of *in situ* cases.

Analyses using either the full cohort or those with interviews, with internal comparisons

Internal exposure–response analyses using a nested case–control design were conducted using Cox regression for the entire cohort (n = 7576) and for the sub-cohort with interviews (n = 5139). Analyses were done using the SAS PHREG procedure [11]. Breast cancer ascertainment in the sub-cohort with interviews was considered complete, and analyses based on interviews were able to include variables for reproductive risk factors.

In these analyses the time variable was age (effectively matching on age), and risk sets were constructed in which 100 randomly selected controls were chosen for each case from the pool of all those who survived without breast cancer to at least the age of the index case; 100 controls has been shown to be sufficient to obtain a good approximation of the rate ratio obtained using all possible controls (the full risk set), with approximately the same precision [12]. Cases and controls were matched on race (white/non-white).

Exposure in these analyses was truncated if it extended beyond the age of the case failure.

For the analysis of the sub-cohort with interviews, we considered variables thought a priori to be associated with breast cancer and hence to be possible confounders, including body mass index, breast cancer in a first-degree relative, parity, age at menopause, age at menarche, socioeconomic status, and diet. Of these only parity and breast cancer in a first-degree relative proved to be important predictors of breast cancer, and only these were included in final models. Menopausal status was considered a possible effect modifier and analyzed as such.

Exposure–response analyses in Cox regression focused on cumulative exposure or the log of cumulative exposure, with or without a lag for exposure. The log of cumulative exposure tends to reduce the influence of very high exposures in skewed exposure distributions, and sometimes improves fit over untransformed cumulative exposure. We also tried models using peak exposure (highest one time exposure) or average exposure (cumulative exposure divided by duration of exposure).

To investigate further the shape of the exposure-response curve, we conducted a restricted cubic-spline analysis with six knots. This analysis fitted a cubic exposure–response curve between knots, while fitting a linear model before and after the first and last knots [13].

Results

Completed interviews were obtained for 5139 (68%) of the 7576 women in the cohort. The principal reason for no interview was inability to locate the respondent (22%), rather than refusal (7%), or failure to respond after repeated attempts (3%). Reasons for not locating women or their next-of-kin included a lack of good addresses for tracing next-of-kin of deceased subjects (we had no SSNs, the best identifier, for next-of-kin), and the lack of recent or valid addresses for live subjects provided from IRS or credit bureaus (often several years out of date).

Of the entire cohort, the average duration of exposure was 10.7 years (s.d. 9.2), and 1327 (18%) had died. Interviews were available (from next-of-kin) for 55% of decedents, compared to 71% among the living. Non-respondents had a median year of birth of 1937, and had a median cumulative dose to ETO of 8.0 ppm-years; the corresponding figures for respondents were 1938 and 8.6 ppm-years. While the level of non-response (32%) is of concern, we attempted to determine breast cancer incidence for the entire cohort *via* sources other than the interview, and a number of analyses were based on the entire cohort. Furthermore, results for the entire cohort (incomplete ascertainment) were similar to the results for the sub-cohort with interviews (complete ascertainment).

Table 1. Source of breast cancer cases (n = 319)

Source (more than one source per case possible)	Number of cases identified by source (%)
Death certificates	95 (30)
Cancer registries	182 (57)
Medical record[a]	144 (45)
Interview (live)[b]	147 (46)
Interview (dead)[b]	60 (19)

[a] Eighty-five percent with histopathology confirmation in the record.

[b] Two hundred and thirty three breast cancer cases or their next-of-kin had interviews. Medical record or cancer registry confirming their breast cancer was found for 189 of these (81%). Twenty-five interviews did not indicate that the respondent or the decedent (for next of kin interviews) had breast cancer on the interview (some next-of-kin did not answer this question), but breast cancer was found *via* medical record or cancer registry data. Six other women or their next-of-kin reported breast cancer on interview, but these reports were contradicted by medical record or cancer registry record; these women were therefore not considered cases.

There were 319 incident breast cancers identified among the cohort through the end of 1998, who were eligible for the study (diagnosed after one year after first employment and 90 days exposure). Table 1 provides information regarding the source of these 319 cases. Thirty-nine percent (124/319) of these cases had died by the end of 1998. Six percent were carcinoma-*in situ* cases (n = 20). Seventy-three percent (n = 233) had interview data. Although breast cancer was ascertained for 30% of cases from death certificates, this was the only source for only 14% of cases; therefore for only 14% of cases did we use date of death as date of diagnosis.

Table 2 provides some descriptive information on cases and non-cases from among those who had

Table 2. Description of cases and non-cases with interview data[a]

Variable	Cases (n = 233)	Non-cases (n = 4906)
% Nulliparous	15.0%	11.6%
% With first-degree relative with breast cancer	16.3%	10.3%
% Pre-menopausal at diagnosis	14.4%	n.a.
Mean year of birth	1932 (s.d. 11.3)	1938 (s.d. 12.6)
Mean number of children	2.29 (s.d. 3.52)	2.36 (s.d. 3.34)
Mean BMI age 20	20.8 (1.6)	21.0 (1.6)
Median cumulative exposure	14.0 ppm-years	8.4 ppm-years
Means years exposed	13.0 (s.d. 9.2)	10.9 (s.d. 9.4)

[a] Based on those with complete interview data for parity and breast cancer in first degree relatives. Somewhat fewer subjects had complete data for menopausal status and BMI.

Table 3. Rate ratios for breast cancer incidence by cumulative exposure to ETO (ppm-days), life table and Poisson regression analyses of entire cohort (n = 7576)

	0 (lagged out)	<647	647–2026	2026–4919	4919–14,620	>14,620	Combined exposed	Test for trend, for cum. exp. or log cum. exp.[b]
15 year lag								
External referent[a]	0.88 (0.67–1.04)	0.77 (0.56–1.03)	0.77 (0.56–1.03)	0.94 (0.69–1.25)	0.83 (0.61–1.11)	1.27 (0.94–1.69)	0.89 (0.78–1.01)	Linear, $p = 0.002$ log $p = 0.05$
Observed cases[c]	81	45	46	46	45	48	230	
		<855	855–2596	2596–6343	6343–16,447	>16,447		
No lag								
External referent[a]	n.a.	0.74 (0.57–0.97)	0.81 (0.62–1.04)	0.92 (0.70–1.18)	0.91 (0.70–1.17)	1.02 (0.79–1.30)	0.87 (0.77–0.97)	Linear, $p = 0.16$ log $p = 0.08$
Observed cases		60	62	63	62	64	311	

[a] External referent is US population, SEER cancer incidence rates, 1970–1998, indirectly SIRs stratified for age (5 year categories), ethnicity (white/non-white), and calendar time (5 year categories).
[b] Test for trend (internal referent) calculated *via* Poisson regression, adjusted for age (5 year categories), calendar time (5 year categories), ethnicity (white/non-white).
[c] Three hundred and eleven (of 319) cases were included; eight cases were diagnosed before 1970 when SEER rates became available.

interview data. Cases were older, had fewer children, and were more likely to have had a first-degree relative with breast cancer.

Table 3 provides the results of the life-table analysis of breast cancer incidence for the whole cohort. Overall the cohort had a SIR of 0.87 (0.94 when *in situ* cases were excluded). However, the true number of breast cancers was under-ascertained, so that the SIR based on external SEER comparison rates is underestimated. Regarding exposure-response trends, for the data with a 15 year lag there is a positive trend of higher SIRs ratios with higher cumulative exposure ($p = 0.002$ for cumulative exposure, $p = 0.05$ using the log of cumulative exposure). For the unlagged data, the trend with cumulative exposure was less marked ($p = 0.16$ for cumulative exposure, $p = 0.08$ using the log of exposure).

Results of internal analyses using all cases (319 cases, including 20 *in situ* cases) are shown in Table 4 (adjusted only for year of birth and age). In categorical analyses using a 15-year lag, the top quintile had an odds ratio of 1.74 (95% CI: 1.16–2.65). The best fitting model with exposure as a continuous variable was one using the log of cumulative exposure, lagged 15 years ($p = 0.05$). However, a model using duration of exposure (with a 15 year lag) fit slightly better than the model using cumulative exposure to ETO. Duration of exposure and cumulative exposure are correlated (Spearman correlation coefficient 0.36). Models using peak or average exposure did not fit as well and are not shown.

Internal analysis for those with interviews (n = 5139, 233 cases) are shown in Table 5. These models are adjusted for parity (any children *versus* none), breast cancer in a first-degree relative, and year of birth (quartiles). The results in Table 5 are concordant with Table 4, although exposure response coefficients were slightly higher and the models using the log of cumulative exposure (lagged 15 years) and untransformed cumulative exposure (lagged 15 years) fit about equally well. Duration of exposure (with a 15 year lag) again fit slightly better than cumulative exposure to ETO in a model using continuous variables.

Of the 233 cases with interviews, menopausal status was unknown or missing for 38, was pre-menopausal for 28, and was post-menopausal for 167. Using a model with log cumulative exposure (15 year lag), year of birth, breast cancer in first degree relatives, and parity, the exposure–response coefficient was 0.051 (s.e. 0.024, $p = 0.04$) for post-menopausal women, and 0.036 (s.e. 0.041, $p = 0.34$) for pre-menopausal women.

Figure 1 shows the exposure–response curves for the full cohort (n = 7576, 319 cases) based on internal analyses (units are ppm-days). The figure shows the

Table 4. Odds ratios for breast cancer incidence by cumulative exposure to ETO (ppm-days), Cox regression analyses[a] of entire cohort (n = 7576, 319 cases)

Exposure variable	Coefficient, (s.d.), *p*-value	Odds ratios by category[b]
Categorical, cumulative exposure lagged 15 years (quintiles)	n.a.	1.00 (lagged out), 1.07 (0.72–1.59), 1.00 (0.67–1.50), 1.24 (0.85–1.90), 1.17 (0.78–1.78), 1.74 (1.16–2.65)
Categorical, cumulative exposure, no lag (quintiles)	n.a.	1.00, 0.98 (0.69–1.38), 1.07 (0.76–1.51), 1.13 (0.80–1.59), 1.16 (0.82–1.65)
Categorical, duration of exposure, lagged 15 years (quintiles)	n.a.	1.00, 0.98 (0.66–1.45), 1.15 (0.77–1.73), 1.37 (0.91–2.04), 1.10 (0.73–1.67), 1.91 (1.22–2.15)
Continuous, log cumulative exposure lagged 15 years	0.037 (0.019), $p = 0.05$	n.a.
Continuous, log cumulative exposure	0.049 (0.034), $p = 0.14$	n.a.
Continuous, cumulative exposure, lagged 15 years	0.0000054 (0.0000035), $p = 0.12$	n.a.
Continuous, cumulative exposure	0.0000013 (0.0000030), $p = 0.66$	n.a.
Continuous, duration exposure, lagged 15 years	0.028 (0.02), $p = 0.02$	n.a.
Continuous, duration exposure	0.012 (0.008), $p = 0.17$	n.a.

[a] Odds ratios calculated *via* Cox regression, cases and controls matched on age, ethnicity (white/non-white), all models include cumulative exposure and categorical variable for year of birth (quartiles).
[b] Categories for cumulative exposure are the same as Table 3.

Table 5. Odds ratios for breast cancer incidence by cumulative exposure to ETO (ppm-days), Cox regression analyses[a] of cohort with interviews (n = 5139, 233 cases)

Exposure variable	Coefficient, (s.e.), *p*-value	Odds ratios by category[b]
Categorical, cumulative exposure lagged 15 years (quintiles)	n.a.	1.00 (lagged out), 1.06 (0.66–1.71), 0.99 (0.61–1.60), 1.24 (0.76–2.00), 1.42 (0.88–2.29), 1.87 (1.12–3.10)
Categorical, cumulative exposure, no lag (quintiles)	n.a.	1.00, 1.25 (0.83–1.88), 1.19 (0.78–1.83), 1.52 (1.00–2.29), 1.41 (0.92–2.16)
Categorical, duration of exposure, lagged 15 years (quintiles)	n.a.	1.00, 1.00 (0.63–1.60), 1.18 (0.73–1.90), 1.39 (0.86–2.25), 1.11 (0.67–1.82), 2.32 (1.37–3.94)
Continuous, log cumulative exposure lagged 15 years	0.050 (0.023), $p = 0.03$	n.a.
Continuous, log cumulative exposure	0.092 (0.041), $p = 0.02$	n.a.
Continuous, cumulative exposure, lagged 15 years	0.0000095 (0.0000041), $p = 0.02$	n.a.
Continuous, cumulative exposure	0.0000059 (0.0000035), $p = 0.10$	n.a.
Continuous, duration exposure, lagged 15 years	0.039 (0.014), $p = 0.006$	n.a.
Continuous, duration exposure	0.019 (0.010), $p = 0.07$	n.a.

[a] Odds ratios calculated *via* Cox regression, cases and controls matched on age, ethnicity (white/non-white), all models include cumulative exposure and categorical variables for year of birth (quartiles), breast cancer in first-degree relative, and parity.
[b] Categories for cumulative exposure are the same as Table 3.

categorical data, and three different models (cumulative exposure, log of cumulative exposure, and the spline curve). It is visually apparent that the log of cumulative exposure fits the categorical data and corresponds well with the spline curve.

While biological considerations do not generally favor the possibility of thresholds for carcinogens (exposure levels below which there is no risk), we also tested a threshold model. The best fitting threshold model (6.2 log ppm-days with a 15 year lag, equivalent to 1.3 years of exposure under the current standard of 1 ppm) was not a statistical significant improvement over the non-threshold model (model likelihood 25.9 *versus* 24.0, respectively).

The dip in the spline curve in the region of higher exposures suggested an inconsistent or non-monotonic risk with increasing exposure. Further categorical analyses using deciles of cumulative exposure (with a 15 year

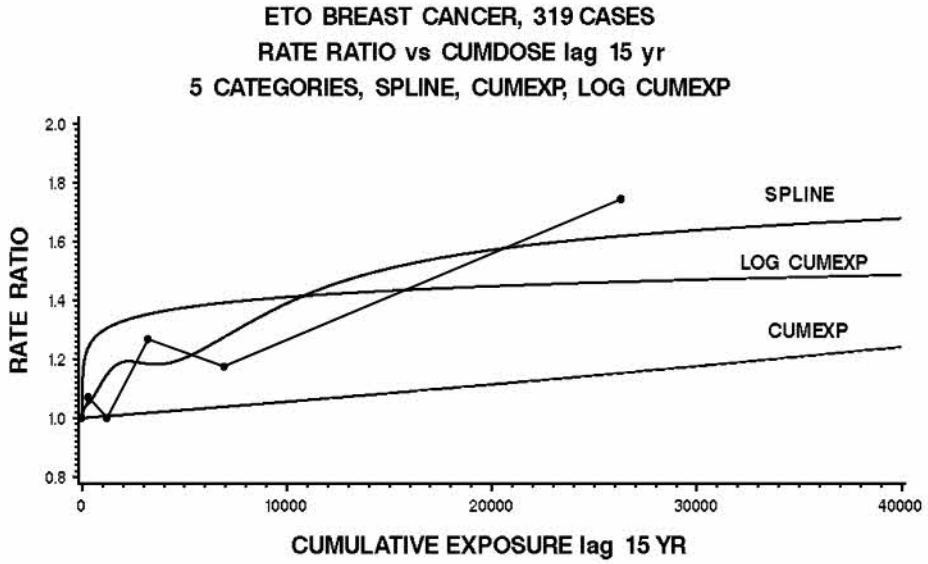

Fig. 1. Exposure–response curves, internal analysis.

lag) rather than quintiles revealed that the 8th decile had no excess risk (odds ratios by decile *versus* those lagged out, 0.88, 1.35, 1.00, 1.00, 1.33, 1.22, 1.40, 1.03, 1.68, 1.82).

There were at least two possible biases which might have biased our results towards higher breast cancer rates among the more highly exposed. First, women with longer cumulative exposure tend to be those who worked longer (Spearman correlation, 0.36), and workers with longer employment may have had more screening *via* mammography because they had good medical surveillance and insurance coverage (although women who left employment with a study company may well have found other employment elsewhere with equally good medical benefits). We had some limited data on mammography for live respondents. After excluding women with breast tumors lumps, or cysts, who would have had more mammograms subsequent to such problems, and after controlling for age, we did not find a strong association between cumulative exposure (in quintiles) and number of mammograms (0, 1–5, 6–10, 10+) *via* contingency table analysis ($p = 0.25$). Furthermore the Spearman correlation coefficient between cumulative dose and number of mammograms (categories scored 0, 1, 2, 3) was low, only 0.08. Thirty-nine percent of women in the highest exposure quintile had more than five mammograms, *versus* 30% of women in the low exposure quintile. Restriction of the data to those with at least five years after exposure, when this possible bias might be expected to diminish, did not result in decreased exposure-response trends. All in all, there was no strong evidence (based on limited data) that this bias was important.

A second possible bias was the preferential ascertainment of breast cancer among women with stable residence in states with cancer registries; women with stable residency might be expected to have longer duration of employment in companies under study, and hence greater cumulative exposure. Unfortunately, we did not have residential history, limiting our ability to explore this possibility. We did, however, compare the cumulative exposure of women whose cancer was ascertained *via* cancer registry ($n = 182$) and women whose cancer was ascertained only *via* other records ($n = 137$). Cumulative exposure was greater in the cases ascertained *via* cancer registry, but this difference was not statistically significant ($p = 0.13$). Again, we did not consider this to be strong evidence, based on limited data, for this potential bias.

Discussion

Our data do not indicate any overall excess of breast cancer incidence among the cohort as a whole compared to the US population. However, cancer incidence was under-ascertained because of inability to locate some cohort members and because of incomplete coverage of the cohort by state cancer registries. We were able to contact only 68% of our cohort directly, and only about 50% of the cohort worked in states with cancer registries covering many years. It is not possible to accurately estimate the degree of under-ascertainment. Even with the under-ascertainment, however, we did find that those in the upper quintile of cumulative exposure, with

a 15 year lag, had a 27% increase in breast cancer incidence compared to the SEER non-exposed population (34% after excluding *in situ* cases).

Because of the issue of under-ascertainment, we have emphasized internal exposure-response analyses in our study rather than the use of external referent population. Exposure-response data do suggest an increased risk of incident breast cancer for those with higher cumulative exposures to ETO. This is especially apparent for exposures occurring 15 or more years before breast cancer occurrence.

Those in the top quintile of cumulative exposure, with a 15 year lag, showed an odds ratio of 1.74 (95% CI: 1.16–2.65) in internal analyses based on all 319 cases compared with the lagged out group. The odds ratio was 1.87 (95% CI: 1.12–3.10) in a similar analysis based on 233 cases with interview data, which controlled for parity and breast cancer in first degree relatives. Less excess risk for the upper quintile was seen without the lag. However, use of a lag is consistent with a necessary latency period for solid tumors. The best fitting models for the exposure-response trend used a lag of 15 years and a log transformation of cumulative exposure, and showed statistically significant positive trends. The log transformation implies that rate ratios tend to flatten out or plateau at very high exposures, rather than increasing in a linear fashion. This phenomenon has been seen in other occupational carcinogens such as dioxin, silica, and diesel fumes [14–16], and has been discussed in detail in relation to arsenic [17].

There are two factors which tend to weaken the case for a causal relationship suggested by the positive exposure–response findings. One is that similar effects were seen using duration of exposure rather than cumulative exposure. This raises the possibility that some other factor related to duration of exposure could be associated with increased breast cancer risk, rather than cumulative exposure to ETO. Secondly, the increase in risk did not increase consistently (monotonically) with increasing cumulative exposure, especially in categorical analyses with 10 categories.

On the other hand, there are counter-arguments to these weaknesses. Since duration of exposure is one component of cumulative exposure, the two are necessarily correlated (Spearman correlation coefficient 0.36), and it is not unexpected for exposure–response trends to exist for both measures. There are many uncertainties in estimating past exposures based on limited actual measurements. We did not have measured exposure levels for each person in our study, but instead estimated exposure levels over time based on existing measurement for different job categories. The method undoubtably led to errors in estimating exposure for individuals. Errors in estimating exposure can lead to similar imprecision in estimating exposure-response trends. However, imperfect exposure estimation is typical of most retrospective epidemiologic studies. The exposure estimation for this cohort was based on a relatively large number of existing samples and is probably one of the better examples in the literature of retrospective exposure assessment. Our model predictions out-performed the best guesses of a panel of industrial hygienists assembled to evaluate our exposure prediction model [9].

Regarding the inconsistency of the exposure-response trend, it is not uncommon for such trends to exhibit fluctuations, some of which may be due to random variation, others of which might occur due to imprecision in estimating exposure.

There was evidence supporting a positive exposure-response from mortality data for women through 1998 for this same cohort [18]. The overall breast cancer standardized mortality ratio (SMR) for the 9885 women in the original NIOSH cohort (without the one year employment restriction) was unremarkable (SMR 0.99, 102 deaths). Exposure–response analyses indicated the highest exposure quartile had an SMR of 1.27 based on 26 deaths. When a 20-year lag was applied, the highest exposure quartile had an SMR of 2.07 (95% CI: 1.10–3.54, based on 13 deaths).

In summary, our data do suggest that ETO exposure is associated with increased incidence of breast cancer. However, there are some inconsistencies in the exposure-response data, and there are possible biases due to patterns of non-response and cancer ascertainment which introduce additional uncertainties in the findings. Exposure levels to ETO in the US have decreased greatly since the early 1980s when a one ppm standard was instituted.

Acknowledgements

Comments on the manuscript were kindly provided by Tom Smith, Ellen Eisen, and Louise Brinton, as well as reviewers from several companies in the study and the American Chemistry Council.

References

1. NIOSH (1989) *National Occupational Exposure Survey: sampling methodology*. Cincinnati, OH: DHHS publication NIOSH, pp. 89–102.
2. IARC (1994) *Some Industrial Chemicals, Monograph 60*. Lyon, France: IARC.
3. Norman S, Berlin J, Soper K, Middendorf B, Stolley P (1995) Cancer incidence in a group of workers potentially exposed to ethylene oxide. *Int J Epidemiol* **24**: 276–284.

4. Tompa A, Major J, Jakab M (1999) Is breast cancer cluster influenced by environmental and occupational factors among hospital nurses in Hungary? *Pathol Oncol Res* **2**: 117–121.
5. Hagmar L, Welinder H, Linden K, *et al.* (1991) An epidemiological study of cancer risk among workers exposed to ETO using hemoglobin adducts to validate environmental exposure assessments. *Occ Environ Health* **63**: 271–277.
6. Hogstedt C, Aringer L, Gustavsson A (1986) Epidemiologic support for ETO as a cancer-causing agent. *JAMA* **255**: 1575–1578.
7. Gardner M, Coggon D, Pannett B, *et al.* (1989) Workers exposed to ETO: a follow-up study. *Brit J Ind Med* **46**: 860–865.
8. Steenland K, Stayner L, Griefe A, *et al.* (1991) A cohort mortality study of workers exposed to ethylene oxide. *New Engl J Med* **324**(20): 1402–1407.
9. Hornung R, Greife A, Stayner L, *et al.* (1994) Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. *Am J Ind Med* **25**: 825–836.
10. Steenland K, Spaeth S, Cassinelli R, Laber P, Chang L, Koch K (1998) NIOSH Life Table Program for Personal Computers. *Am J Ind Med* **34**: 517–518.
11. SAS (1991) *SAS User's Guide*: *Statistics* (*Version 6.07*). NC: SAS Institute Cary.
12. Steenland K, Deddens J (1997) Increased precision using countermatching in nested case–control studies. *Epidemiology* **8**: 238–242.
13. Harrell F, Lee K, Pollock B (1988) Regression models in clinical studies: determining relationships between predictors and response. *JNCI* **80**: 1198–1202.
14. Steenland K, Deddens J, Piacitelli L (2001) Risk assessment for 2,3,7,8-*p*-dioxin (TCDD) based on an epidemiologic study. *Am J Epidemiol* **154**: 451–458.
15. Steenland K, Mannetje A, Boffetta P, *et al.* (2001) Pooled exposure–response and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multi-centric study. *Cancer Causes Control* **12**: 773–784.
16. Steenland K, Deddens J, Stayner L (1998) Diesel exhaust and lung cancer in trucking industry: exposure–response analyses and risk assessment. *Am J Ind Med* **34**: 220–228.
17. Hertz-Piccioto I, Smith A (1993) Observations on the dose–response curve for arsenic exposure and lung cancer. *Scand J Work Environ Health* **19**: 217–226.
18. Steenland K, Stayner L, Deddens J (2003) Mortality analyses in a cohort of 18,235 ethylene oxide-exposed workers: follow-up extended from 1987 to 1998. Occup Env Med, in press.

Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998

K Steenland, L Stayner and J Deddens

Occup. Environ. Med. 2004;61;2-7

ORIGINAL ARTICLE

Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998

K Steenland, L Stayner, J Deddens

Occup Environ Med 2004;**61**:2–7

See end of article for authors' affiliations

Correspondence to: Dr N K Steenland, Rollins School of Public Health, Emory University, 1518 Clifton Road, Atlanta, GA 30322, USA; nsteenl@sph.emory.edu

Accepted 11 January 2003

Aims: To extend mortality follow up from 1987 to 1998 for cohort of 18 235 men and women exposed to ethylene oxide.
Methods: Standard mortality follow up, life table and Cox regression analysis.
Results: There were 2852 deaths, compared with 1177 in the earlier 1987 follow up. There was no overall excess of haematopoietic cancers combined or of non-Hodgkin's lymphoma. However, internal exposure-response analyses found positive trends for haematopoietic cancers which were limited to males (15 year lag). The trend in haematopoietic cancer was driven by lymphoid tumours (non-Hodgkin's lymphoma, myeloma, lymphocytic leukaemia), which also have a positive trend with cumulative exposure for males with a 15 year lag. Haematopoietic cancer trends were somewhat weaker in this analysis than trends in the earlier follow up, and analyses restricted to the post-1987 data did not show any significant positive trends (exposure levels dropped sharply in the early 1980s). Breast cancer did not show any overall excess, although there was an excess in the highest cumulative exposure quartile using a 20 year lag. Internal exposure-response analyses found positive trend for breast cancer using the log of cumulative exposure with a 20 year lag.
Conclusions: There was little evidence of any excess cancer mortality for the cohort as a whole, with the exception of bone cancer based on small numbers. Positive exposure-response trends for lymphoid tumours were found for males only. Reasons for the sex specificity of this effect are not known. There was also some evidence of a positive exposure-response for breast cancer mortality.

Ethylene oxide (ETO) is widely used as a sterilant gas and an industrial chemical. NIOSH has estimated that approximately 270 000 people were exposed in the USA in the 1980s, principally in hospitals (96 000) and commercial sterilisation (21 000).[1] ETO is a direct alkylating agent which causes increased chromosomal aberrations and sister chromatid exchange.[2] Inhaled ETO is quickly absorbed in the lungs and distributed rapidly throughout all tissues; it forms dose related haemoglobin adducts in people and rodents, and dose related DNA adducts have been measured in rodents.[2] The International Agency for Research on Cancer (IARC) determined in 1994 that ETO was a definite (group 1) human carcinogen, based on limited evidence from epidemiological studies showing increased haematopoietic cancers which was supported by positive human cytogenetic evidence, and on sufficient evidence from animal studies for haematopoietic and other cancers.[2]

Ethylene oxide has been studied in 10 cohort studies with over 33 000 workers. The largest component is the cohort studied here (18 000). Results of these studies as of 1998 were reviewed by Teta and colleagues.[3] Generally cancer findings were unremarkable in comparisons of exposed workers to the general population for most of these studies, with the notable exception of large excesses of haematopoietic cancer (particularly leukaemia) in several early small studies from Sweden. However, a meta-analysis of all 10 studies did show an increase in non-Hodgkin's lymphoma (1.34, 95% CI 0.96 to 1.89), based on 33 deaths.

Besides haematopoietic cancer, more recently there has been concern that ETO might also be linked to breast cancer, based on limited evidence. Norman and colleagues[4] found a statistically significant twofold increase in breast cancer incidence based on 12 observed cases among women exposed at a plant doing commercial sterilisation of medical products. A cluster of breast cancers was observed among Hungarian hospital workers exposed to ETO.[5] Furthermore, animal data indicated that ETO caused mammary tumours in mice,[2] although not in rats. However, two other small incidence studies (together based on fewer than 10 cases) did not show an excess of breast cancer.[6 7] Two mortality studies, one small[8] (four breast cancer deaths) and one large[9] (the present cohort, 42 breast cancer deaths as of 1987) also failed to show an excess.

In the mid 1980s the National Institute for Occupational Safety and Health (NIOSH) assembled a cohort of 18 235 workers exposed to ethylene oxide.[9 10] Results of the original follow up through 1987 showed no overall excess of haematopoietic cancer, but did find a significant excess among men (SMR 1.55, 1.02–2.26), concentrated in non-Hodgkin's lymphoma (NHL).[9] Exposure-response analyses showed a significant positive trend with cumulative exposure for lymphoid cancers (non-Hodgkin's lymphoma and lymphocytic leukaemia, ICD 9th revision codes, 200, 202, 204), particularly among men.

We have updated the vital status of this cohort from 1987 to 1998. This resulted in 2852 deaths, a 140% increase over the 1177 deaths in the earlier follow up. Analyses focused on haematopoietic and breast cancer mortality. A study of breast cancer incidence is the subject of a different paper.[11]

METHODS

Vital status follow up was conducted through 1998 via the National Death Index (NDI), which provided cause of death, and via the Social Security Administration and the Internal Revenue Service (IRS). Person-time for each subject began

Abbreviations: ETO, ethylene oxide; NHL, non-Hodgkin's lymphoma; SMR, standardised mortality ratio

Main messages

- There was little evidence of cancer excesses for the ethylene oxide exposed workers versus the general population in this 11 year update of the largest existing cohort of ETO workers.
- However, positive exposure-response trends were found for males for lymphoid cancer mortality, and for females for breast cancer mortality.
- Male and female workers of each sex with the highest cumulative exposures and longest latency had statistically significant excesses for these two cancers, respectively.
- There is priori evidence from other studies, both animal and human, associating these cancers with ETO.

90 days after first exposure (due to a three month minimum for cohort eligibility), and continued until 31 December 1998, date of death, or date of loss to follow up, whichever was earlier. Life table analyses were conducted using the NIOSH life table program (Steenland *et al*, 1998), which allows for calculations of standardised mortality ratios (SMRs) for 99 causes of death for the years 1960–99. Deaths and person-time prior to 1960 were not included in this analysis, but there were only eight deaths before 1960 (0.2% of all deaths).

Exposure data over time for this cohort had been developed previously, based on a large number of measurements coupled with data of historical process changes, making it possible to quantitatively estimate cumulative exposure to ethylene oxide.[12] One small plant in the study (n = 705, 4% of the cohort) lacked exposure estimates, and was excluded from exposure-response analyses. Exposure levels generally diminished sharply in the early 1980s after the reports of a haematopoietic cancer effect in animals and humans.

Work history data had been gathered originally in the mid-1980s. Some plants in the study continued using ETO after this point. For those plants, we gathered additional information on the date last employed for those who had been employed and exposed at the time work history was collected (25% of the cohort). Work history for these individuals was extended until the date last employed at the plant; it was assumed that they did not change jobs and that the level of ETO exposure remained the same as in their last job in the mid-1980s. This represented a compromise between an expensive and time consuming effort to update all work histories in detail, and ignoring the incomplete histories altogether. In practice when we compared cumulative exposure calculated with and without the extended work histories, they differed little, largely because exposures were very low by the mid-1980s, so that the largest proportion of cumulative exposure came before those years.

Life table analyses were conducted for the entire cohort (n = 18 235), using the US population as the referent population.[13] Categorical analyses were done after categorising the data by quartiles of cumulative exposure, based on distribution of cumulative exposure for either the deaths from either haematopoietic cancer or from breast cancer. The goal was to have approximately equal numbers of deaths from the principal causes of interest (haematopoietic and breast cancer) in each quartile, in unlagged analyses, thereby ensuring approximately equal precision of rate ratios. Life table analyses were conducted using no lag, a 10 year lag for haematopoietic cancer, or a 20 year lag for breast cancer, prostate cancer, and kidney cancer. A 20 year lag discounts all exposure occurring with the last 20 years, and in some instances results in a case having no exposure (''lagged out''). These lags were chosen a priori as typical for haematopoietic tumours and solid tumours. Prostate and kidney cancer analyses were conducted based on finding slight excesses in the overall exposed versus non-exposed analysis, rather than an a priori hypothesis; the same cut points were used in categorical analyses of cumulative exposure as were used for breast cancer, another solid tumour.

Internal exposure-response analyses were conducted using Cox regression for haematopoietic and breast cancer. Cox regression analyses were done using the SAS PHREG procedure.[14] In these analyses the time variable was age (effectively matching on age), and risk sets were constructed in which 100 randomly selected controls were chosen for each case from the pool of all those who survived without haematopoietic or breast cancer to at least the age of the index case. Use of 100 controls has been shown to result in virtually the identical rate ratio with all possible controls (the full risk set), with approximately the same precision,[15] while making possible more rapid computer runs. We refer to the measures of effect from the nested case-control approach (equivalent to a conditional logistic regression analysis) as odds ratios, which estimate that hazard or rate ratio expected from a full Cox regression. Cases and controls were matched on race (white/non-white), sex, and date of birth (within five years), and only exposure variables were included in models. Matching on date of birth, in combination with the use of age as the time variable to form risk set, was equivalent to matching on calendar time. Exposure in these analyses was time dependent, and was truncated if it extended beyond the age of the case failure. Internal analyses focused on cancers of a priori interest—that is, all haematopoietic cancers and breast cancer. We also analysed lymphoid cell line tumours as a group, under the hypothesis that these tumours might share a common aetiology. In previous analyses[10] we had included as lymphoid tumours both non-Hodgkin's lymphoma and lymphocytic leukaemia (9th revision ICD codes 200, 202, and 204), and we again have provided some results for that original grouping. However, we have now also conducted analyses after adding myeloma (ICD code 203) to the lymphoid group, based on current thinking on this issue[16 17] (personal communication, Bernard Goldstein, University of Pittsburgh, 2002). Another complication was that 4/25 (16%) leukaemias in the exposure-response analyses were classified as ''not specified'', some of which might have been lymphocytic leukaemia. Finally, a separate analysis was also done of Hodgkin's disease (ICD 201), although numbers for this cause were quite small.

Exposure-response analyses focused on cumulative exposure or the log of cumulative exposure, with or without a lag for exposure (5, 10, 15, and 20 year lags were tried). A lag period is a period before death or end of follow up during which any exposure is ignored; its use is similar to requiring a latency period. We added 1 ppm-day to cumulative exposure in lagged analyses to avoid taking the log of 0. In the results we present only the lagged model with the best fit to the data, as judged by the likelihood ratio test. We also tried models using peak exposure, average exposure, and duration of exposure, with no lag or different lags. Test of significance for the coefficients of continuous exposure variables (tests for trend) were based on the likelihood ratio statistic rather than the Wald statistic.

RESULTS

Cumulative exposure averaged 26.9 ppm-years in this cohort (SD 65.7), with a highly skewed distribution (median 5.6 ppm-years). Exposure for males (mean 37.8, SD 87.6, median 7.6) was higher than for females (mean 18.2, SD 38.2, median 4.6), largely because of their more frequent

Table 1 Mortality in the ETO cohort (n = 18 235*)

Cause (ICD-9 code)	Observed deaths	SMR (95% CI)	Male SMR (95% CI)	Female SMR (95% CI)
All causes	2852	0.90 (0.88–0.93)	0.94 (0.89–0.99)	0.86 (0.81–0.91)
Coronary heart disease (410–414)	669	0.92 (0.86–0.98)	1.04 (0.85–1.04)	0.87 (0.78–0.99)
All cancers (140–208)	860	0.98 (0.92–1.03)	0.94 (0.95–1.16)	0.92 (0.84–1.01)
Stomach (151)	25	1.07 (0.74–1.49)	0.87 (0.44–1.52)	1.34 (0.71–2.29)
Pancreas (157)	38	0.92 (0.69–1.21)	1.03 (0.64–1.61)	0.82 (0.45–1.30)
Lung (162)	258	1.05 (0.95–1.17)	1.05 (0.89–1.23)	1.05 (0.86–1.27)
Prostate (185)	37	1.29 (0.91–1.78)	1.29 (0.91–1.78)	n.a.
Kidney (189.0–189.2)	21	1.19 (0.80–1.72)	1.51 (0.85–2.49)	0.78 (0.281.28)
Brain (191–192)	14	0.59 (0.36–0.91)	0.52 (0.19–1.13)	0.65 (0.25–7.37)
Bone (170)	6	2.82 (1.23–5.56)	3.51 (0.96–8.98)	2.04 (0.25–7.37)
Breast cancer (174)	103	0.99 (0.84–1.17)	2.04 (0.05–11.37)	0.99 (0.81–1.20)
All haematopoietic (200–208)	79	1.00 (0.79–1.24)	1.09 (0.79–1.47)	0.91 (0.84–1.25)
Non-Hodgkin's lymphoma (200, 202)	31	1.00 (0.72–1.35)	1.29 (0.78–2.01)	0.73 (0.38–1.29)
Hodgkin's disease (201)	6	1.24 (0.53–2.43)	1.83 (0.59–4.27)	0.47 (0.05–11.87)
Myeloma (203)	13	0.92 (0.54–0.87)	0.61 (0.17–1.56)	1.19 (0.54–2.26)
Leukaemia (204–208)	29	0.99 (0.71–1.36)	0.97 (0.52–1.63)	1.02 (0.57–1.68)

*These analyses include the entire cohort. Subsequent exposure-response analyses are based on a reduced cohort in which one small plant (4% of cohort) without adequate exposure data was not included.

employment in high exposure jobs such as steriliser operator or warehouse employee. There were 461 000 person years of follow up; mean follow up time from first employment was 26.8 years (SD 8.5). Sixteen per cent of the cohort died during follow up, which ended on 31 December 1998. Of the decedents, 1.5% (n = 44) were missing cause of death.

Table 1 gives the overall mortality results for the entire cohort, compared to the US population. No cancer site showed a significant excess at the 0.05 level, with the exception of bone cancer, for which there were only six deaths. Neither all haematopoietic cancer nor non-Hodgkin's lymphoma show any increase. In sex specific analyses, the rate ratios for men for all haematopoietic cancer, leukaemia, and non-Hodgkin's lymphoma were 1.09 (0.79–1.47), 0.97 (0.53–1.63), and 1.29 (0.78–2.01) respectively, while the corresponding rate ratios for women were 0.90 (0.64–1.25), 1.02 (0.57–1.68), and 0.73 (0.38–1.28). Brain cancer mortality, which was of some a priori interest due to positive animal studies, was significantly reduced in this update, similar to findings in our prior follow up. Prostate and kidney cancer showed slight increases (SMR 1.29 (95% CI 0.96 to 1.70, 37 deaths) and 1.19 (95% CI 0.80 to 1.72, 21 deaths), respectively), motivating further life table exposure-response analyses.

Exposure-response analyses were of limited value for bone cancer due to the small number of deaths (n = 6). Life table analyses of bone cancer by quartiles of cumulative exposure (not shown) were not supportive of a positive exposure-response.

Table 2 shows the analyses by quartile of cumulative exposure for all haematopoietic cancer, with the quartiles chosen in order to approximately distribute the haematopoietic deaths equally by quartile. There is no suggestion of a trend for all haematopoietic cancers combined or any specific category, with the exception of Hodgkin's disease where inference is limited by the small number of deaths. Table 3 shows the same analyses with a 10 year lag. Here the highest quartile of cumulative exposure shows a somewhat increased rate ratio for non-Hodgkin's lymphoma, based on nine deaths.

Table 4 shows the data for haematopoietic cancer by sex, with a 10 year lag. The only statistically significant excess, at the 0.05 level, is the SMR for males for non-Hodgkin's lymphoma in the uppermost exposure quartile with a 10 year lag (SMR 2.37, 95% CI 1.02 to 4.67, eight deaths). Five of the six Hodgkin's disease deaths occurred among males, and this outcome again shows a positive exposure-response based on very small numbers. Complementary analyses by 10+ years latency gave similar results. For NHL, the SMRs by quartile were 0.34, 0.78, 1.16, and 2.15 based on 1, 2, 3, and 8 cases, respectively.

Table 5 shows the data for cumulative exposure and breast, prostate, and kidney cancer mortality. The quartiles for these analyses used the quartile cut points which allocated breast cancers equally by quartile. In this analysis there is an indication of excess risk for breast cancer in the uppermost quartile, which is 2.20 (95% CI 1.57 to 2.98) using a 20 year lag. There was little or no suggestion of positive exposure-response trends for prostate or kidney cancer.

Table 6 shows the results of internal Cox regression analyses for all haematopoietic cancers combined, for both sexes combined and for men and women separately. It indicates that only males show positive trends. The best fitting model shows a positive trend (p = 0.02) for males using the log of cumulative exposure with a 15 year lag. The log transformation tends to give less influence in the model to very high exposures typical of skewed exposure distributions, which may improve model fit. It also usually implies that rate ratios tend to flatten out or plateau at higher exposures, rather than increasing in a linear fashion, which is

Table 2 SMRs (observed deaths) by cumulative exposure for haematopoietic cancer (ICD 9th revision 200–208), no lag (n = 17 530)

Cause	0–1199 ppm-days	1200–3679 ppm-days	3680–13499 ppm-days	13500+ ppm-days
All haematopoietic	0.77 (18)	1.31 (20)	1.10 (18)	0.94 (18)
NHL	0.76 (7)	1.34 (8)	0.85 (6)	1.21 (9)
Hodgkin's	0 (0)	0.99 (1)	2.97 (3)	2.20 (2)
Leukaemia	1.15 (10)	1.06 (6)	0.93 (6)	0.43 (3)
Myeloma	0.26 (1)	1.89 (5)	0.92 (3)	1.03 (4)

Table 3 SMRs (observed deaths) by cumulative exposure for haematopoietic cancer, 10 year lag* (n = 17 530)

Cause	0 (lagged out)	>0–1199 ppm-days	1200–3679 ppm-days	3680–13499 ppm-days	13500+ ppm-days
All haematopoietic	0.72 (9)	0.88 (18)	1.16 (15)	1.08 (16)	1.04 (16)
NHL	1.31 (5)	0.71 (6)	1.13 (6)	0.66 (4)	1.47 (9)
Hodgkin's	0.41 (1)	0 (0)	1.75 (1)	3.57 (2)	3.77 (2)
Leukaemia	0.40 (2)	1.35 (10)	0.85 (4)	1.33 (7)	0.36 (2)
Myeloma	1.36 (1)	3.65 (2)	2.44 (4)	1.03 (3)	0.92 (3)

*A 10 year lag ignores any exposure which occurs in the ten years prior to death or end of follow up.

Table 4 SMRs (observed deaths) by cumulative exposure, for haematopoietic cancer mortality, by sex, 10 year lag

Cause	0 (lagged out)	>0–1199 ppm-days	1200–3679 ppm-days	3680–13499 ppm-days	13500+ ppm-days
Males (n = 7645)					
All haematopoietic	1.15 (7)	0.63 (5)	0.87 (5)	1.10 (7)	1.46 (13)
NHL	2.09 (4)	0.61 (2)	0.88 (2)	0.79 (2)	2.37* (8)
Hodgkin's	1.07 (1)	0 (0)	3.44 (1)	3.44 (1)	5.71 (2)
Leukaemia	0.41 (1)	1.01 (3)	0.0 (0	1.70 (4)	0.60 (2)
Myeloma	1.56 (1)	0 (0)	1.94 (2)	0 (0)	0.54 (1)
Females (n = 9885)					
All haematopoietic	0.31 (2)	1.04 13)	1.38 (10)	1.06 (9)	0.46 (3)
NHL	1.88 (1)	0.78 (4)	1.32 (4)	0.56 (2)	0.37 (1)
Hodgkin's	0 (0)	0 (0)	0 (0)	3.70 (1)	0 (0
Leukaemia	0.49 (1)	1.57 (7)	1.56 (4)	1.02 (3)	0 (0)
Myeloma	0 (0)	0.85 (2)	1.42 (2)	1.76 (3)	1.43 (2)

*95 % CI 1.02 to 4.67.

Table 5 SMRs (observed deaths) by cumulative exposure, for breast cancer, prostate cancer, and kidney cancer, no lag and 20 year lag

Cause	0 (lagged out)	>0–646 ppm-days	647–2779 ppm-days	2780–12321 ppm-days	12322+ ppm-days
Breast—no lag (females only)		1.00 (26)	0.85(24)	0.92 (26)	1.27 (26)
Prostate—no lag		1.74 (6)	1.47 (8)	0.77 (5)	1.33 (15)
Kidney—no lag		0.88 (3)	0.74 (3)	1.36 (6)	1.06 (5)
Breast—20 year lag (females only)	0.80 (42)	1.05 (17)	1.01 (15)	1.15 (15)	2.07* (13)
Prostate—20 year lag	1.08 (8)	1.43 (5)	1.44 (6)	1.75 (8)	1.00 (7)
Kidney—20 year lag	0.70 (2)	0.28 (1)	1.62 (6)	2.11 (8)	0.99 (5)

*95% CI 1.10 to 3.54.

apparent in our own data here for males. Categorical analyses by quartile for males indicated that all three upper quartiles were increased compared to the lowest category. Categorical analyses using cumulative exposure with a 15 year lag shows a more monotonically increasing trend.

Although not shown, models using duration of exposure, peak exposure, and average exposure did not predict haematopoietic cancer as well as models using cumulative exposure.

Table 7 shows result for lymphoid tumours. There is a positive trend for lymphoid tumours (non-Hodgkin's lymphoma, myeloma, and lymphocytic leukaemia) with cumulative exposure for both sexes combined ($p = 0.08$), which was again concentrated in for males ($p = 0.06$ for cumulative exposure and $p = 0.02$ for log cumulative exposure, 15 year lag, the latter being the best fitting model). Although not shown, models using duration of exposure, peak exposure, and average exposure did not predict haematopoietic cancer as well as models using cumulative exposure.

Additional analyses (not shown) were conducted using a more restricted definition of lymphoid tumours (non-Hodgkin's lymphoma and lymphocytic leukaemia, $n = 40$, 23 male and 17 female deaths) to conform to our earlier analysis of this cohort.[10] The coefficient for cumulative exposure with no lag was 5.6×10^{-6} (SE 2.3×10^{-6}, $p = 0.04$, based on change in likelihood), decreased from 9.0×10^{-6} in our earlier follow up which ended in 1987. ETO exposure levels dropped sharply in the 1980s following reports of leukaemia, and this may have contributed to decreased haematopoietic cancer after 1987.

Additional regression analyses, not shown, were restricted to the period following 1987, the end of the prior follow up. In these post-1987 analyses there were no significant positive trends for all haematopoietic cancer ($n = 41$), male haematopoietic cancer ($n = 13$), lymphoid cancers ($n = 31$), or male lymphoid cancers ($n = 10$). The analyses restricted to males did show a suggestion of increased haematopoietic cancer, but analyses were limited by small numbers. The coefficient for male haematopoietic cancer for log cumulative exposure with a 15 year lag was 0.11 (SE 0.12, $p = 0.35$), about the same value as that for the entire follow up period (table 7).

Additional analyses (not shown) were conducted for Hodgkin's disease, based on only six deaths. A positive trend ($p = 0.08$) was found for the log of cumulative exposure with a lag of 10 years, for both sexes combined. This excess also was concentrated in males (five of six deaths).

Table 8 gives the results for internal Cox regression analyses for breast cancer. The best model using a continuous exposure variable was that using the log of cumulative exposure with a 20 year lag ($p = 0.01$). Cumulative exposure itself did not show a strong trend ($p = 0.16$). Categorical analysis of lagged data (20 year lag) showed an increased rate in the highest quartile (3.13, 95% CI 1.42 to 6.92).

Table 6 Cox regression* results for all haematopoietic cancer mortality

Analysis, exposure variable	Model likelihood, df, p value†	Coefficient (SE)	Odds ratios by category‡
Both sexes, cumulative exposure	1.62, 1 df, p=0.20	0.0000033 (0.0000023)	
Males, cumulative exposure	2.45, 1 df, p=0.12	0.0000040 (0.0000022)	
Males, categorical cumulative exposure	2.53, 3 df, p=0.46	na	1.00, 2.07 (0.67–6.41), 2.02 (0.68–5.98), 2.06 (0.72–5.91)
Females, cumulative exposure	0.87, 1 df, p=0.34	−0.000011 (0.000014)	
Females, categorical cumulative exposure	3.78, 3 df, p=0.29	na	1.00, 1.51 (0.69–3.34), 0.93 (0.38–2.30), 0.52 (0.16–1.66)
Males, log cumulative exposure, 15 year lag	5.29, 1 df, p=0.02	0.119 (0.052)	
Males, categorical cumulative exposure, 15 year lag	6.81, df=4 p=0.15	na	1.00, 1.23 (0.32–4.73), 2.52 (0.69–9.22), 3.13 (0.95–10.37, 3.42 (1.09–10.73)

*Cases and controls matched on age, race (white/non-white), date of birth within five years, 74 cases (37 male, 37 female).
†Model likelihood is difference in −2 log likelihoods between model with and without covariates; the only covariate in these models was exposure, so the p value of the model serves as a test of significance of the exposure coefficient, and as a test of exposure-response trend.
‡Categories for cumulative exposure are the same as in tables 2–5.

Table 7 Cox regression results for lymphoid cell line tumours*

Analysis, exposure variable	Model likelihood, df, p value†	Coefficient (SE)	Odds ratios by category‡
Both sexes, cumulative exposure	3.16, 1 df, p=0.08	0.0000046 (0.0000022)	na
Males, cumulative exposure	3.62 1 df, p=0.06	0.0000050 (0.0000022)	na
Males, categorical cumulative exposure	2.43, 3 df, p=0.49	na	1.00, 2.45 (0.61–9.92, 1.85 (0.46–7.48), 2.44 (0.67–8.87)
Females, cumulative exposure	0.08, 1 df, p=0.78	−0.0000034 (0.000012)	na
Females, categorical, cumulative exposure	2.81, 3 df, p=0.42	na	1.00, 2.05 (0.76–5.56), 1.25 (0.40–3.76), 0.87 (0.24–3.10)
Males, log cumulative exposure, 15 year lag	5.39, 1df, p=0.02	0.138 (0.061)	na
Males, categorical cumulative exposure, 15 year lag	6.62, 4 df, p=0.13	na	1.00, 0.90 (0.16–5.24), 2.89 (0.65–12.86) 2.74 (0.65–11.55), 3.76 (1.03–13.64)

*Lymphoid cell line tumours include NHL, myeloma, and lymphocytic leukaemia (ICD 9th revision codes 200, 202, 203, 204 (53 cases, 27 male, 26 female). Cox regression, cases and controls matched on age, race (white/non-white), date of birth within five years.
†Model likelihood is difference in −2 log likelihoods between model with and without covariates; the only covariate in these models was exposure, so the p value of the model serves as a test of significance of the exposure coefficient, and as a test of exposure-response trend.
‡Categories for cumulative exposure are the same as in tables 2–5.

Table 8 Cox regression results for breast cancer mortality*

Analysis, exposure variable	Model likelihood, df, p value†	Coefficient (SE)	Odds ratios by category‡
Cumulative exposure	0.88, 1 df, p=0.34	0.0000049 (0.0000048)	na
Log cumulative exposure, 20 year lag	5.69, 1df, p=.01	0.084 (0.035)	na
Categorical cumulative exposure lagged 20 years (quartiles)	8.69, 4 df, p=0.07	na	1.00, 1.76 (0.91–3.43), 1.77 (0.88–3.56), 1.97 (0.94–4.06), 3.13 (1.42–6.92)

*There were 103 cases of breast cancer (ICD 9th 174, 175). In Cox regression, cases and controls were matched on age, race (white/non-white), and date of birth within five years.
†Model likelihood is difference in −2 log likelihoods between model with and without covariates; the only covariate in these models was exposure, so the p value of the model serves as a test of significance of the exposure coefficient, and as a test of exposure-response trend.
‡Categories for cumulative exposure are the same as in table 6.

DISCUSSION

We have now updated mortality follow up for the large NIOSH cohort of 18 000 workers exposed to ethylene oxide, adding 11 more years of follow up and more than doubling the number of deaths. There was no evidence of cancer excesses in exposed versus non-exposed comparisons, with the exception of bone cancer. The healthy worker effect has diminished (all cause mortality was up to an SMR of 0.90 from the prior SMR of 0.81), as would be expected with increased follow up. The healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons.

There was a significant excess of bone cancer compared to the US population, based on only six deaths, but this excess did not show an increase with increasing exposure. There is some supporting animal evidence in that mice injected subcutaneously developed local sarcomas,[2] which share the mesenchymal cell origin of bone tumours. However, due the small number of bone cancer deaths, and the lack of exposure-response, no conclusions can be drawn from this excess. No other cancer site was in excess in the cohort.

Regarding haematopoietic cancer, we did not find an overall excess of haematopoietic cancer or any specific type of haematopoietic cancer. However, we did find statistically

significant exposure-response trends for male haematopoietic cancer, particularly lymphoid tumours. These findings are consistent with analyses of this cohort with earlier follow up.[10] Exposure-response coefficients were somewhat smaller than we found in our earlier analyses (analyses restricted to recent years did not show significant positive exposure-response trends). This suggests that any ETO damage to the haematopoietic system may be decreasing over time.

It is not known why we find an association for males and not females for haematopoietic cancer. While males on average did have higher exposure than females because they were over-represented in high exposure jobs (for example, steriliser operator), there was sufficient variation in the exposure of women to have observed an exposure-response if one existed. Animal data do not support a sex-specific effect for leukaemia.

The increasing trends in rate ratios for haematopoietic or lymphoid cancer for males, and breast cancer for females, were fit best by a model using a log transformation of cumulative exposure rather than untransformed cumulative exposure. Use of the log gives less weight to extremely high exposures which often occur in log-normal distribution typical of occupational studies, and a log transformation tends to fit better when rate ratios tail off or plateau at very high exposures. This phenomenon has been seen in other occupational carcinogens such as dioxin,[18] silica,[19] and diesel fumes,[20] and has been discussed in detail in relation to arsenic.[21] Possible reasons for this phenomenon include, among others: (1) a depletion of susceptibles at high exposures, (2) the healthy worker survivor effect, (3) misclassification of high exposures, and (4) a saturation of metabolic pathways.

While we considered a large number of models in our exposure-response analyses, we believe that this type of extensive search for the best model is appropriate in this situation—that is, it is not an example of "data dredging" or the perils of multiple hypothesis testing. For example, we knew from previous experience that a latency period is likely to be required for cancer (hence the lagging), and that the log of cumulative exposure often fits better than cumulative exposure itself in occupational cancer studies. Hence we believe it was appropriate to search for the best fitting lag and to try the log of cumulative exposure.

We found no overall excess of breast cancer mortality, but we did find a suggestive positive trend with increasing cumulative exposure, particularly after taking into account a 20 year lag period. Mortality is a less sensitive endpoint than incidence for breast cancer. We have also recently completed a study of breast cancer incidence in this cohort, results of which confirm a positive trend of increased breast cancer with increased cumulative exposure.[11]

Our study had a number of limitations, including the reliance on small numbers to make inferences about haematopoietic cancers, uncertainties in the retrospective estimation of exposure, and the use of mortality data rather than incidence data for evaluation of cancer risk. On the other hand, this is by far the largest existing cohort of ETO workers, the 11 year update has added substantially more deaths, and retrospective exposure estimation for this study was based on a large number of observed industrial hygiene samples and a well validated model to estimate past exposures. Mortality data for haematopoietic cancer might be expected to give similar results to incidence data, as these cancers are often fatal.

In conclusion, we found no overall evidence of excess cancer mortality in this cohort, with the exception of bone cancer based on small numbers. However, in exposure-response analyses we found evidence of an association between increased exposure and some types of haematopoietic cancer, particularly for males. There is also some evidence for a positive exposure-response for breast cancer mortality.

ACKNOWLEDGEMENTS

Harvey Checkoway, Elizabeth Whelan, Tom Soraan, and Olav Axelson kindly provided comments on this manuscript.

Authors' affiliations

K Steenland, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA
L Stayner, J Deddens, National Institute for Occupational Safety and Health (NIOSH), Cincinnati, Ohio, USA

REFERENCES

1 **NIOSH**. *National Occupational Exposure Survey: sampling methodology*. Publication NIOSH 89-102. Cincinnati, OH: DHHS, 1989.
2 **IARC**. *Some industrial chemicals*. Monograph 60. Lyon, France: IARC, 1994.
3 **Teta J**, Sielken R, Valdez-Flores C. Ethylene oxide cancer risk assessment based on epidemiologic data: application of revised regulatory guidelines. *Risk Analysis* 1999;**19**:1135–55.
4 **Norman S**, Berlin J, Soper K, *et al*. Cancer incidence in a group of workers potentially exposed to ethylene oxide. *Int J Epidemiol* 1995;**24**:276–84.
5 **Tompa A**, Major J, Jakab M. Is breast cancer cluster influenced by environmental and occupational factors among hospital nurses in Hungary? *Pathology Oncology Research* 1999;**2**:117–21.
6 **Hagmar L**, Welinder H, Linden K, *et al*. An epidemiological study of cancer risk among workers exposed to ETO using hemoglobin adducts to validate environmental exposure assessments. *Occup Environ Health* 1991;**63**:271–7.
7 **Hogstedt C**, Aringer L, Gustavsson A. Epidemiologic support for ETO as a cancer-causing agent. *JAMA* 1986;**255**:1575–8.
8 **Gardner M**, Coggon D, Pannett B, *et al*. Workers exposed to ETO: a follow-up study. *Br J Ind Med* 1989;**46**:860–5.
9 **Steenland K**, Stayner L, Griefe A, *et al*. A cohort mortality study of workers exposed to ethylene oxide. *N Engl J Med* 1991;**324**:1402–7.
10 **Stayner L**, Steenland K, Greife A, *et al*. Exposure-response analyses of cancer mortality in a cohort of workers exposed to ethylene oxide. *Am J Epidemiol* 1993;**138**:787–8.
11 **Steenland K**, Whelan E, Deddens J, *et al*. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women. *Cancer Causes Control* 2003;**14**:531–9.
12 **Hornung R**, Greife A, Stayner L, *et al*. Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. *Am J Ind Med* 1994;**25**:825–36.
13 **Steenland K**, Spaeth S, Cassinelli R, *et al*. NIOSH Life Table Program for Personal Computers. *Am J Ind Med* 1998;**34**:517–18.
14 SAS, *SAS user's guide: statistics (version 6.07)*. Cary, NC: SAS Institute, 1991.
15 **Steenland K**, Deddens J. Increased precision using counter-matching in nested case-control studies. *Epidemiology* 1997;**8**:238–42.
16 **Cotran R**, Kumar V, Collins T, eds. *Pathologic basis of disease*. Philadelphia: Saunders, 1999.
17 **Harris N**, Jaffe E, Diebold J, *et al*. WHO classification of neoplastic diseases of the hematopoietic and lymphoid tissues. *J Clin Oncol* 1999;**17**:3835–49.
18 **Steenland K**, Deddens J, Piacitelli L. Risk assessment for 2,3,7,8-*p*-dioxin (TCDD) based on an epidemiologic study. *Am J Epidemiol* 2001;**154**:451–8.
19 **Steenland K**, Mannetje A, Boffetta P, *et al*. Pooled exposure-response and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multi-centric study. *Cancer Causes Control* 2001;**12**:773–84.
20 **Steenland K**, Deddens J, Stayner L. Diesel exhaust and lung cancer in trucking industry: exposure-response analyses and risk assessment. *Am J Ind Med* 1998;**34**:220–8.
21 **Hertz-Piccioto I**, Smith A. Observations on the dose-response curve for arsenic exposure and lung cancer. *Scand J Work Environ Health* 1993;**19**:217–26.

From:	Curwin, Brian D. (CDC/NIOSH/DSHEFS)
To:	Jinot, Jennifer
Cc:	Lin, Yu-Sheng
Subject:	RE: questions regarding the NIOSH ethylene oxide exposure data
Date:	Wednesday, April 22, 2015 1:27:00 PM
Attachments:	SKMBT_C55015042213070.pdf SKMBT_C55015042213050.pdf

Hi Jennifer,

Attached are a couple of documents that I hope provide the answers you need. Let me know if this isn't it.

Brian

From: Jinot, Jennifer [mailto:Jinot.Jennifer@epa.gov]
Sent: Thursday, April 16, 2015 9:58 AM
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Cc: Lin, Yu-Sheng
Subject: RE: questions regarding the NIOSH ethylene oxide exposure data

hi, Brian. i am just following up on this earlier inquiry. we were wondering if you had had any luck obtaining the code definitions for the departments and operations. without those, it will be hard to try to figure out what might explain some of the changes in exposure levels over time, so if you are able to provide those, we would really appreciate it. thanks!
jennifer

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS) [mailto:bic4@cdc.gov]
Sent: Tuesday, March 24, 2015 11:05 AM
To: Jinot, Jennifer
Cc: Lin, Yu-Sheng
Subject: RE: questions regarding the NIOSH ethylene oxide exposure data

Hi Jennifer,

Unfortunately I am not familiar with the data at all. For questions 1, 2, and 4 you may want to ask Kyle Steenland these questions. If he cannot answer, I am not sure who could. I will check on the code definitions.

Brian

From: Jinot, Jennifer [mailto:Jinot.Jennifer@epa.gov]
Sent: Friday, March 20, 2015 3:05 PM
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Cc: Lin, Yu-Sheng; Jinot, Jennifer

Subject: questions regarding the NIOSH ethylene oxide exposure data

hi, Brian. a colleague, Yu-Sheng Lin, who was listed on the DUA, has been looking at the exposure data that you sent us earlier this year, and we have a few questions about the data that we were hoping you could answer.

1. Are we correct to interpret these exposure values as predictions from the Hornung et al. exposure regression model for different plants/operations/time periods?

2. What is the exposure unit for daily ethylene oxide exposure? Are these 8-hour TWA exposures in ppm?

3. Can we please get the code definitions for both the "Department" and "Operation" codes?

4. Is there any information for the ethylene oxide cohort study as to the use of personal protection equipment (PPE), such as respiratory masks, by the sterilizer workers? Or can we assume that there was no use of PPE for the sterilizer workers during the time period of 1938-1986?

thank you very much for any help that you can provide in responding to these questions.
regards,
jennifer

From: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
To: Jinot, Jennifer
Subject: RE: ethylene oxide mortality dataset
Date: Thursday, May 21, 2015 4:42:00 PM

Yes, that would be ok, provided the data does not have any identifying information or any data that would otherwise not be allowed to be released.

From: Jinot, Jennifer [mailto:Jinot.Jennifer@epa.gov]
Sent: Thursday, May 21, 2015 3:30 PM
To: Curwin, Brian D. (CDC/NIOSH/DSHEFS)
Subject: ethylene oxide mortality dataset

Hi, Brian. [redacted]

[redacted]

Thanks, jennifer